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Chordoid meningioma represents a rare meningioma variant. It is histologically defined by presence of trabeculae of eosinophilic and vacuolated epithelioid cells within a mucin-rich stroma [7]. The term chordoid meningioma was first used by Kepes et al. in 1988 [5], who published a series of seven cases. In a subsequent larger series of 42 cases, a considerable risk of recurrence even after total resection was identified [4]. Based on these findings, chordoid meningiomas are per definition graded as WHO grade II [7].

For several variants of meningioma, associations with distinct genetic events have been identified. Examples are *KLF4/TRAF7* mutations in secretory meningioma, enrichment for *AKT1* mutations in meningothelial meningioma, *SMARCE1* mutations in clear cell meningioma, and *BAP1* mutation or deletion in rhabdoid meningioma [2,3,9,12] [11]. So far, no distinct mutation has been identified for chordoid meningioma. Also, no unique DNA methylation pattern has been found for chordoid meningioma [8,10]. For angiomatous, metaplastic, and microcystic meningioma, an association with gain of chromosome 5 has been reported [1,6]. Therefore, we sought to identify potential characteristic chromosomal alterations associated with chordoid histology. We compiled a cohort of 40 patients with chordoid meningiomas. Clinical follow-up data were available of 30 patients, DNA methylation data of 38 patients (Suppl. Table 1), both clinical follow-up and DNA methylation data were obtained for 28 patients. Tissue and clinical data were used in accordance with local ethical approval. Methods are described in the supplementary material. Meningiomas with chordoid differentiation were most common in frontal falx localization (Suppl. Table 1). All cases were reviewed according to the WHO classification 2016. None of these chordoid meningiomas had criteria for WHO grade II other than chordoid histology. All but one had chordoid differentiation in >50% of the respective tumor specimens, one single case presented with chordoid morphology in only 40% of the embedded material.

Chordoid meningiomas showed significant enrichment for deletions of chromosomal arm 2p ($p<0.0001$): While 17/38 (45%) chordoid meningioma had 2p deletion, only 66/526 (12.5%) meningiomas of other subtypes carried this aberration ($p<0.0001$, Fig 1a-b, Suppl. Table 1, 2). The enrichment for deletion of 2p was still evident when restricting the control group to WHO grade II (Fig 1c).

We next sought to test the value of chordoid morphology for prediction of outcome in the 30 patients with available clinical follow-up data in comparison to a cohort of 192 meningioma patients with tumors of other subtypes (Suppl. Table 1). Time to tumor recurrence in patients with chordoid meningiomas was significantly worse than in patients with WHO grade I meningiomas ($p=0.01$). In turn, outcome was statistically not different from patients with non-chordoid meningiomas of WHO grade II ($p=0.14$), supporting the current standard of assigning chordoid meningioma to WHO grade II (Fig 1d). Of note, although significantly

associated with chordoid differentiation, deletion of 2p was not an independent predictor of outcome, neither across all patients nor within patients with chordoid meningiomas (Suppl. Fig 1a, b, chordoid meningioma patients in this analysis restricted to the 28 patients with available molecular data and clinical follow-up). As mentioned before, chordoid meningiomas do not fall into a distinct DNA methylation group but dissolve into all clinically relevant subgroups. Of the 38 chordoid meningiomas with DNA methylation data in this cohort, 24 fell into benign Methylation Classes (MCs), 13 into intermediate MCs, one into the MC malignant of meningiomas. As chordoid meningioma are per definition WHO grade II but grouped with MCs of different malignancy, we tested in the 28 patients with follow-up data whether subgrouping of chordoid meningioma by DNA methylation further improves the accuracy of outcome prediction also for this particular histological subtype. Assignment to DNA methylation subgroups was indeed able to predict outcome with higher accuracy than the histological grading (Fig 1e). While the cohort of chordoid meningioma patients on average had an outcome according to patients with other types of WHO grade II meningiomas, DNA methylation-based classification allotted the chordoid meningiomas to subgroups that more precisely predicted clinical outcome (Suppl. Fig 1c, d). This higher predictive power of DNA methylation profiling indicates that subgroups of lower or higher risk of recurrence, respectively, can be identified by epigenetic analysis.

Finally, we assessed whether certain mutations are enriched in chordoid meningioma. Panel sequencing data was already available for 11 samples from previous studies and could be supplemented by data from 10 additional tumors (Suppl. Figure 2). In line with a frequency of 22q deletion below the average of the compound cohort of other meningioma subtypes (Fig 1a-c), *NF2* mutations were comparatively rare with only three (14.3%) mutant cases. *AKT1* or *SMO* hotspot and *TERT* promoter mutations were absent. Four chordoid meningiomas (19%) had isolated *TRAF7* mutations in absence of *KLF4* or *AKT1* mutations, one of those had a 2p deletion. One chordoid meningioma carried a *PIK3CA* hotspot mutation.

While deletion of 2p is significantly associated with chordoid morphology, it is by far not observed in all cases, and also not restricted to chordoid meningioma. In conjunct with the low frequency of otherwise known mutations in meningioma, this points towards additional, as of yet not discovered aberrations in this subtype. However, we were not able to compile a cohort of these rare cases with sufficient high-quality DNA or RNA and matched blood for more comprehensive whole-exome, whole-genome sequencing, or RNA sequencing. Upcoming large consortia dedicated to meningioma research may collect the critical amount of samples in order to pursue these efforts. This may also elucidate further clinical implications of 2p alterations, which cannot yet be inferred from the present data. For now,

our data shows that DNA methylation profiling can improve the diagnostic accuracy of outcome prediction in chordoid meningioma.

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Legend to Figure

Integrated copy number plots for 38 chordoid meningiomas (a), 526 meningiomas across all WHO grades (b), and 166 WHO grade II meningiomas (c) show the enrichment for deletions of 2p in chordoid meningioma. The probability of recurrence-free survival for the chordoid meningioma patients investigated here was statistically not different from that of other WHO grade II meningioma patients (d). In line, separating chordoid meningiomas from other WHO grade II meningiomas does not add to the prediction power of the classification. The stratification for DNA methylation classes, however, strongly increases the predictive power in a Brier prediction plot (e).

References

1 Abedalthagafi MS, Merrill PH, Bi WL et al. (2014) Angiomatous meningiomas have a distinct genetic profile with multiple chromosomal polysomies including polysomy of chromosome 5. Oncotarget 5: 10596-10606

2 Brastianos PK, Horowitz PM, Santagata S et al. (2013) Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. Nat Genet 45: 285-289

3 Clark VE, Erson-Omay EZ, Serin A et al. (2013) Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science 339: 1077-1080

4 Couce ME, Aker FV, Scheithauer BW (2000) Chordoid meningioma: a clinicopathologic study of 42 cases. The American journal of surgical pathology 24: 899-905

5 Kepes JJ, Chen WY, Connors MH, Vogel FS (1988) "Chordoid" meningeal tumors in young individuals with peritumoral lymphoplasmacellular infiltrates causing systemic manifestations of the Castleman syndrome. A report of seven cases. Cancer 62: 391-406

6 Ketter R, Kim YJ, Storck S et al. (2007) Hyperdiploidy defines a distinct cytogenetic entity of meningiomas. Journal of neuro-oncology 83: 213-221

7 Louis DN, Perry A, Reifenberger G et al. (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta neuropathologica 131: 803-820

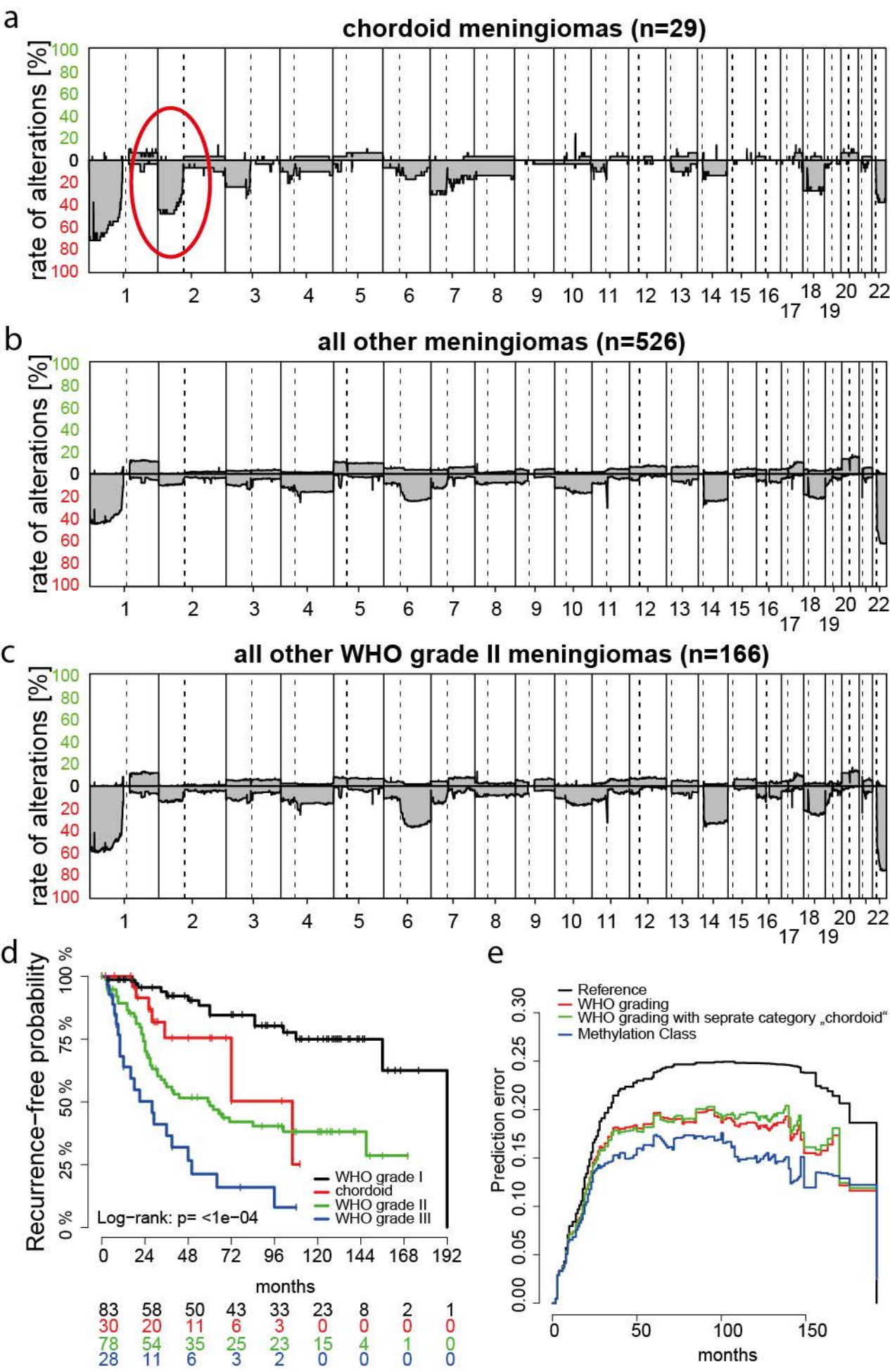
8 Olar A, Wani KM, Wilson CD et al. (2017) Global epigenetic profiling identifies methylation subgroups associated with recurrence-free survival in meningioma. Acta neuropathologica 133: 431-444

9 Reuss DE, Piro RM, Jones DT et al. (2013) Secretory meningiomas are defined by combined KLF4 K409Q and TRAF7 mutations. Acta neuropathologica 125: 351-358

10 Sahm F, Schrimpf D, Stichel D et al. (2017) DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Lancet Oncol 18: 682-694

11 Shankar GM, Abedalthagafi M, Vaubel RA et al. (2017) Germline and somatic BAP1 mutations in high-grade rhabdoid meningiomas. Neuro Oncol 19: 535-545

12 Smith MJ, O'Sullivan J, Bhaskar SS et al. (2013) Loss-of-function mutations in SMARCE1 cause an inherited disorder of multiple spinal meningiomas. Nat Genet 45: 295-298


a
chordoid meningiomas (n=29)
rate of alterations [%]
b
all other meningiomas (n=526)
rate of alterations [%]
c
all other WHO grade II meningiomas (n=166)
rate of alterations [%]
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 22
d
Recurrence−free probability
0 % 25 % 50 % 75 % 100 %
WHO grade I
chordoid
WHO grade II
WHO grade III
Log−rank: p= <1e−04
0 24 48 72 96 120 144 168 192
months
83 58 50 43 33 23 8 2 1
30 20 11 6 3 0 0 0 0
78 54 35 25 23 15 4 1 0
28 11 6 3 2 0 0 0 0
e
Reference
WHO grading
WHO grading with seprate category „chordoid“
Methylation Class
Prediction error
0.00 0.05 0.10 0.15 0.20 0.25 0.30
0 50 100 150
months